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ORIGINAL ARTICLE
Epidemiology & prevention

$P2Y_{12}$ inhibitor versus aspirin monotherapy for secondary prevention of cardiovascular events: meta-analysis of randomized trials

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Aim To compare the efficacy and safety of $P2Y_{12}$ inhibitor or aspirin monotherapy for secondary prevention in patients with atherosclerotic cardiovascular disease (ASCVD).

Methods and results Medline, Embase, and Cochrane Central databases were searched to identify randomized trials comparing monotherapy with a $P2Y_{12}$ inhibitor versus aspirin for secondary prevention in patients with ASCVD (cardiovascular, cerebrovascular, or peripheral artery disease). The primary outcome was major adverse cardiac events (MACE). Secondary outcomes were myocardial infarction (MI), stroke, all-cause mortality, and major bleeding. A random-effects model was used to calculate risk ratios (RR) and the corresponding 95% confidence interval (CI) and heterogeneity among studies was assessed using the Higgins I^2 value. A total of 9 eligible trials (5 with clopidogrel and 4 with ticagrelor) with 61 623 patients were included in our analyses. Monotherapy with $P2Y_{12}$ inhibitors significantly reduced the risk of MACE by 11% (0.89, 95% CI 0.84–0.95, $I^2 = 0\%$) and MI by 19% (0.81, 95% CI 0.71–0.92, I2 = 0%) compared with aspirin monotherapy. There was no significant difference in the risk of stroke (0.85, 95% CI 0.73–1.01), or all-cause mortality (1.01, 95% CI 0.92–1.11). There was also no significant difference in the risk of major bleeding with $P2Y_{12}$ inhibitor monotherapy compared with aspirin (0.94, 95% CI 0.72–1.22, $I^2 = 42.6\%$). Results were consistent irrespective of the $P2Y_{12}$ inhibitor used.

Conclusion $P2Y_{12}$ inhibitor monotherapy for secondary prevention is associated with a significant reduction in atherothrombotic events compared with aspirin alone without an increased risk of major bleeding.

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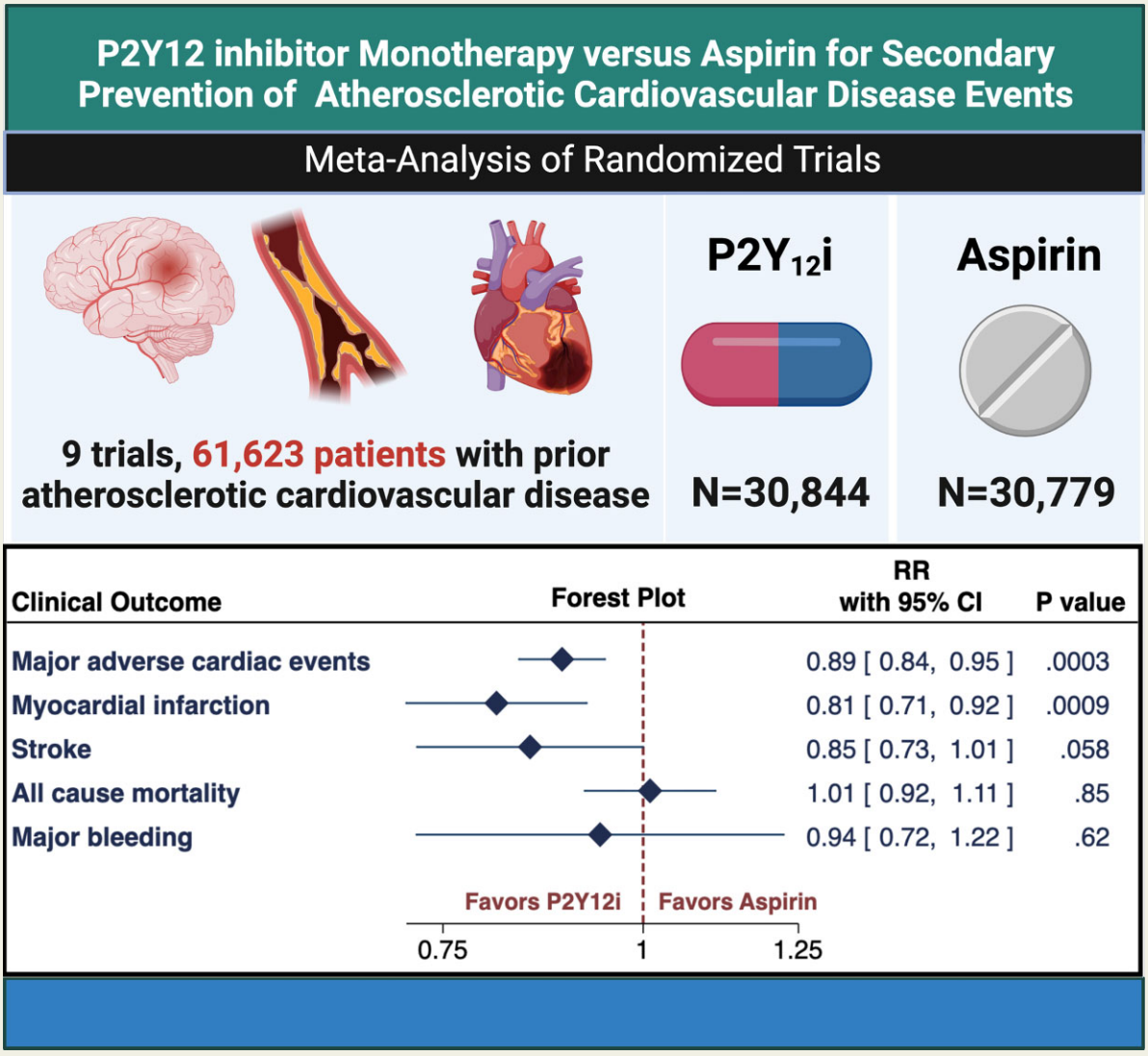
Graphical Abstract



A meta-analysis of 9 randomized trials (61 623 patients) was conducted to compare $P2Y_{12}$ inhibitor monotherapy versus aspirin monotherapy for secondary prevention of cardiovascular events in patients with established atherosclerotic cardiovascular disease (coronary, cerebrovascular, or peripheral artery disease). The included studies had follow-up periods between 3 and 36 months. Monotherapy with $P2Y_{12}$ inhibitors (clopidogrel or ticagrelor) significantly reduced the risk of MACE by 11% (0.89, 95% CI 0.84–0.95, $I^2 = 0\%$) and MI by 19% (0.81, 95% CI 0.71–0.92, $I^2 = 0\%$) compared with aspirin monotherapy. There was no significant difference in the risk of stroke, all-cause mortality, or major bleeding. Subgroup analysis revealed that the reduction in MACE with $P2Y_{12}$ inhibitors was driven by a reduction in recurrence of the qualifying event. CI = confidence interval, P2Y12i = $P2Y_{12}$ inhibitor, RR = risk ratio.

Keywords Atherosclerotic cardiovascular disease • Myocardial infarction • Stroke • Antiplatelet agents • Aspirin • $P2Y_{12}$ inhibitors

Introduction

Antiplatelet therapy is the cornerstone for the prevention and treatment of atherothrombosis.[1–3] Aspirin is the most widely used antiplatelet agent for the prevention of cardiovascular events in patients with atherosclerotic cardiovascular disease.[4,5] $P2Y_{12}$ inhibitors (e.g. clopidogrel, prasugrel, and ticagrelor), when combined with aspirin, provide greater antiplatelet effect and higher efficacy at preventing atherothrombotic events in patients with acute coronary syndromes or in those undergoing percutaneous coronary interventions (PCI).[6–9] In the chronic phase of secondary prevention (i.e. after guideline-recommended duration of dual antiplatelet therapy is completed), $P2Y_{12}$ inhibitors are often discontinued, and aspirin monotherapy is continued for long-term prevention of cardiovascular events. This preferential use of aspirin stems at least partly from insufficient evidence about the risks and benefits of $P2Y_{12}$ inhibitor monotherapy compared with aspirin monotherapy.

Accordingly, we undertook a systematic review and meta-analysis of randomized trials to compare the efficacy and safety of $P2Y_{12}$ inhibitor monotherapy versus aspirin monotherapy for secondary prevention of cardiovascular events in patients with atherosclerotic cardiovascular disease, including coronary, cerebrovascular, or peripheral arterial disease.

Methods

Search strategy and study characteristics

We conducted a comprehensive literature search of multiple electronic databases (Medline, EMBASE, and Cochrane Central) from inception to June 12, 2021. We used the following search terms: 'clopidogrel', 'ticagrelor', 'prasugrel', 'thienopyridine', 'antiplatelet', 'aspirin', 'acetylsalicylic acid', 'prevention', and 'monotherapy' to capture relevant citations. No language restrictions were applied. Presentations at major national cardiovascular meetings and bibliographies of relevant articles were also reviewed. All citations were imported into Covidence[10] and duplicate citations were removed prior to title and abstract review. All studies were screened by 2 reviewers (D.A. and Z.C.) and relevant studies were identified for the full-text review. If there was discordance among reviewers regarding the inclusion of a study in the final analysis, a third reviewer was consulted to reach a consensus (A.Q.). All randomized trials reporting clinical outcomes comparing $P2Y_{12}$ inhibitor monotherapy with aspirin monotherapy for secondary prevention in patients with the established atherosclerotic vascular disease were included in this analysis. Trials with a sample size below 100 participants, trials using ticlopidine in the $P2Y_{12}$ inhibitor arm, and trials with a duration of monotherapy of less than 30 days were excluded. Observational or registry studies were also excluded. Full-texts of all the included trials were then reviewed for inclusion in the final meta-analysis. This review was registered with PROSPERO (CRD 42021260714).

Outcome measures

The primary efficacy outcome of interest was major adverse cardiovascular events (MACE). In the majority of studies, MACE was defined as a composite of stroke, myocardial infarction (MI), or death. The primary safety endpoint was major bleeding. Supplementary material online, *Tables S1 and S2* describe the definitions of MACE and major bleeding outcomes used across the trials. Secondary outcomes assessed included MI, stroke (ischemic/hemorrhagic), and all-cause mortality. Data for the primary and secondary outcomes were extracted by two authors (D.A. and Z.C.) independently using pre-specified electronic forms. Additionally, data on the duration of monotherapy, dosage of aspirin/$P2Y_{12}$ inhibitor, qualifying events, and baseline characteristics of the trial participants were extracted individually.

Statistical analysis

Pooled risk ratios (RR) and the corresponding 95% confidence intervals (CI) were calculated for the primary and secondary outcomes using the DerSimonian and Laird random-effects model.[11] We also performed pre-specified subgroup analysis based on the $P2Y_{12}$ inhibitor used and the qualifying atherothrombotic disease (cardiovascular, cerebrovascular, or peripheral artery disease). Additionally, among studies where the qualifying atherothrombotic disease was stable coronary disease or prior acute coronary syndrome, we evaluated the effect of prior revascularization (PCI, coronary artery bypass grafting [CABG], or mixed) on the thrombotic and safety outcomes. Significant differences between the various subgroups were evaluated using the Qb statistic.[12] Heterogeneity among studies was assessed using the Higgins I^2 value.[12] I^2 values of $<25\%$, 25–75%, and $>75\%$ were considered to represent low, moderate, and high levels of heterogeneity, respectively. A random-effects meta-regression analysis using the empirical Bayes method was conducted to evaluate the association of trial-level variables with the primary efficacy and safety outcomes. Meta-regression model variables were selected a priori and included the duration of follow-up with monotherapy, dosage of aspirin, and the baseline risk in the aspirin arm (expressed as a ratio of event/non-event). Among trials reporting a range of aspirin dose, the higher end of the dose range was considered for the regression model. We also conducted a leave-one-out sensitivity analysis to evaluate the effect of individual trials on the pooled primary and secondary endpoints and to exclude the possibility of a single trial disproportionately affecting the overall outcome. Publication bias and small study bias were assessed visually with funnel plots and Egger's regression test. All *p*-values were two-tailed with statistical significance specified at 0.05 and CI reported at 95% level. Stata version 16 (StataCorp, College Station, Texas) and R package, Metafor, version 3.6.2 (R Foundation) were used for all statistical analyses. The number needed to treat (NNT) was calculated using the pooled RRs. The risk of bias and study quality was assessed using the revised Cochrane risk-of-bias tool.[13] Two authors independently assessed (K.B. and V.J.) each study using 5 domains of bias: (i) randomization process, (ii) deviations from intended interventions, (iii) missing outcomes data, (iv) measurement of the outcome, and (v) selection of the reported results. Each individual trials' overall bias was reported as low risk, some concern, or high risk.

Results

Study characteristics

Of the 6058 results identified in the initial search, 9 randomized trials were selected for the analyses after step-wise review (*Figure 1*).[14–22] The design and baseline characteristics of the individual trials are described in *Table 1*. Five studies compared aspirin with clopidogrel while 4 studies compared aspirin with ticagrelor. Six trials enrolled patients with coronary artery disease including 1 study that randomized patients with previous MI, one with chronic coronary syndromes, 2 with patients after PCI with drug-eluting stent placement, and 2 after CABG. Two studies enrolled patients after a stroke or transient ischemic attack and only 1 study, the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial,[14] included patients with a history of ischemic stroke, prior MI, or symptomatic peripheral artery disease. The included studies had follow-up periods between 3 and 36 months. The GLOBAL LEADERS trial, a clinical study comparing 2 forms of antiplatelet therapy after stent implantation trial[21] was designed to compare dual antiplatelet therapy durations of 1 month versus 12 months. However, in the follow-up period from 12 to 24 months, the control group (dual antiplatelet therapy for 1 year) received aspirin whereas the experimental group (dual antiplatelet therapy for 1 month) received ticagrelor. Similarly, the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial[20] compared dual antiplatelet therapy for 21 days followed by clopidogrel with aspirin monotherapy for 90 days. For these 2 trials, we only included outcomes from the period with monotherapy with $P2Y_{12}$ inhibitors or aspirin in the treatment arms.

Study population

A total of 61 623 patients were included in these analyses. Three studies (CAPRIE, GLOBAL LEADERS, Acute Stroke or Transient

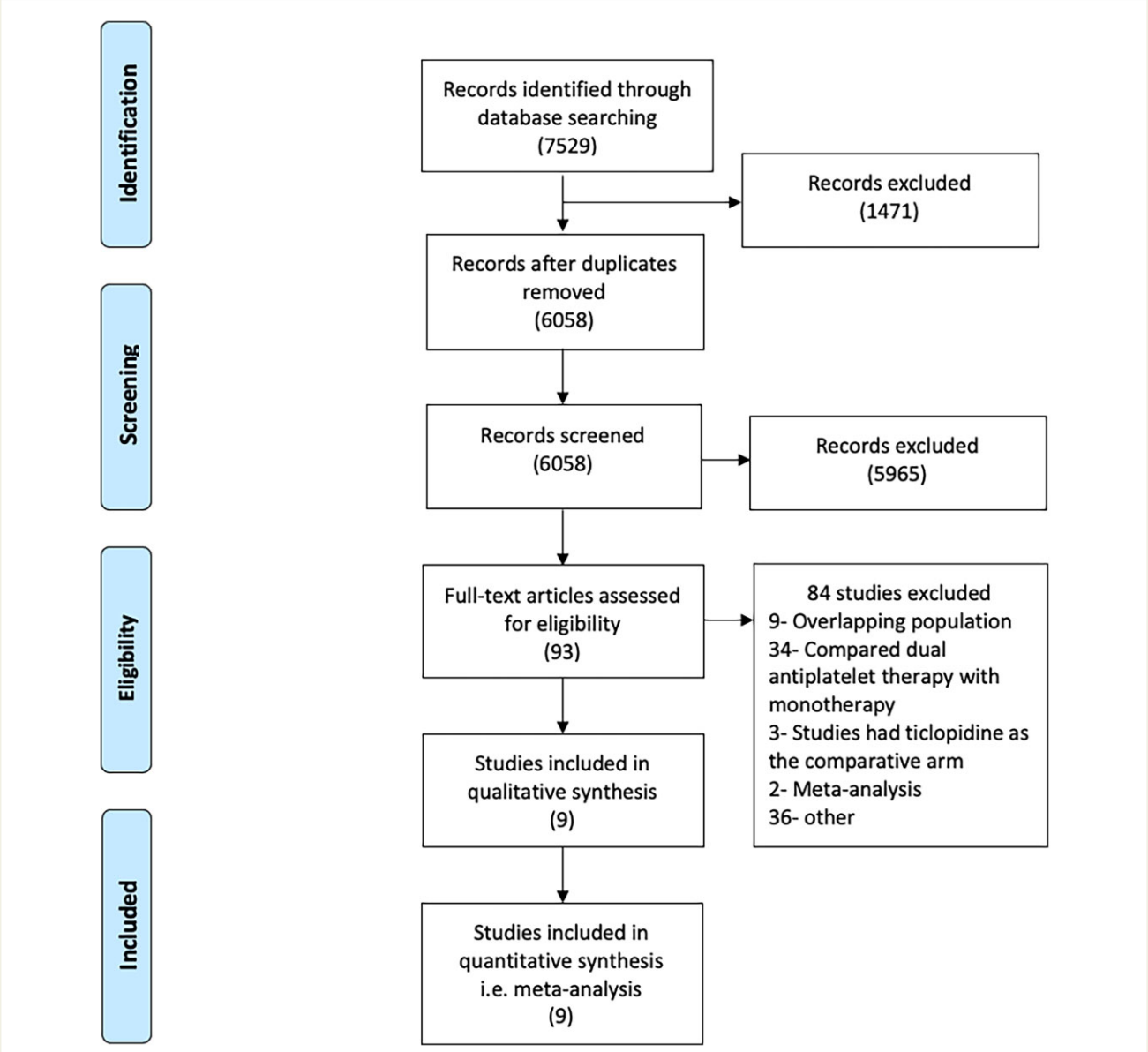


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart for the study. Search of Medline, EMBASE, and Cochrane Central databases revealed 6058 citations. Of these, 9 studies met the inclusion criteria and were included in the analyses.

Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes [SOCRATES]) accounted for more than three-quarters of all patients. The qualifying event for enrolment was stroke in 24 326 (39.5%) patients and acute coronary syndrome in 18 445 (29.9%). 12 400 (20.1%) patients were included due to the presence of chronic coronary syndromes, and 6452 (10.5%) patients were included due to the presence of peripheral artery disease. The mean age of patients was between 62 and 67 years. The proportion of females ranged between 15% and 42%. Although the majority of patients had hypertension, the prevalence of diabetes, chronic kidney disease, and smoking in the different studies was wide-ranging. The most commonly used medications at baseline were statins and beta-blocking agents. Discontinuation rates and/or the proportion of patients lost to follow-up across the studies were generally higher in the $P2Y_{12}$ inhibitor group (see Supplementary material online, *Table S3*).

Outcomes

The primary efficacy outcome (MACE) and safety outcome (major bleeding) are depicted in *Figures 2 and 3*. The risk of MACE was significantly reduced with the use of $P2Y_{12}$ inhibitor monotherapy as compared with aspirin (RR 0.89 [95% CI 0.84–0.95], $I^2 = 0\%$, NNT 141). This result was consistent irrespective of the $P2Y_{12}$ inhibitor used (p-interaction = 0.83). The use of $P2Y_{12}$ inhibitors was also

Table 1 **Study design and baseline characteristics of the included trials.**

Trial name	CAPRIE	ASCET	HOST EXAM	TICAB	GLOBAL LEADERS	CADET	DACAB	SOCRATES	CHANCE
Study design									
Total patients	19185	1001	5438	1859	15968	184	332	13199	5170[a]
Study design	Double blind	Double blind	Open label	Double blind	Open label	Double blind	Open label	Double blind	Double blind
Year of publication	1996	2012	2021	2019	2018	2004	2018	2016	2013
Qualifying event	Stroke, CAD, PAD	Stable CAD	CAD patients post-PCI	CAD patients post-CABG	CAD patients post-PCI	CAD	CAD patients post-CABG	Stroke or high-risk TIA	Stroke or high-risk TIA
Multicentre (Yes/No)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Country	Multinational	Norway	South Korea	Multinational	Multinational	United Kingdom	China	Multinational	China
Treatment arm	Clopidogrel (75 mg once daily)	Clopidogrel (75 mg once daily)	Clopidogrel (75 mg once daily)	Ticagrelor (90 mg twice daily)	Ticagrelor (90 mg twice daily)	Clopidogrel (75 mg once daily)	Ticagrelor (90 mg twice daily)	Ticagrelor (90 mg twice daily)	Clopidogrel (75 mg once daily)
Comparison	Aspirin (325 mg once daily)	Aspirin (75 mg once daily)	Aspirin (100 mg once daily)	Aspirin (100 mg once daily)	Aspirin (75–100 mg once daily)	Aspirin (75 mg once daily)	Aspirin (100 mg once daily)	Aspirin (100 mg once daily)	Aspirin (75 mg once daily)
Duration of monotherapy	36 months	24 months	24 months	12 months	12 months[b]	6 months	12 months	3 months	68 days[c]
Duration of follow-up	36 months	24 months	24 months	12 months	24 months	6 months	12 months	3 months	3 months
Baseline characteristics									
Mean age (SD)	62.5	62.4	63.5 (10.7)	66.7	64.5 (10.3)	62.6	63.6	65.8	62
Females	28.1%	21.8%	25.5%	15.1%	23.3%	19.1%	17.2%	41.6%	33.8%
Hypertension	51.5%	55.4%	61.4%	89.9%	73.6%	–	72.8%	73.7%	65.7%
Diabetes mellitus	20.0%	19.9%	34.2%	35.9%	25.3%	–	42.7%	24.3%	21.1%
Dyslipidemia	41.0%	–	69.3%	81.7%	69.6%	–	73.1%	38.0%	11.1%
Current or previous smoker	78.5%	20.4%	20.7%	55.3%	26.1%	74.5%	48.5%	–	43.0%
CKD		–	12.7%	7.0%	13.7%	–	0.9%	–	–
Previous stroke/TIA	40	–	4.7%	8.9%	2.6%	–	10.5%	100%	23.3%
Prior MI	44%	43.7%	16.0%	22.7%	23.3%	100%	31%	4.1%	1.9
PAD	38%	5.4%	–	9.1%	6.4%	–	16.9%	–	–
Prior PCI	–	73%	–	20.2%	32.7%	–	–	–	–
Prior CABG	–	18.5%	–	0.8%	5.9%	–	24.7%	–	–
Baseline Medication use									
Statins	–	98.3%	–	83.6%	–	78.8%	94.0%	–	42.0%
Beta-blockers	–	75.8%	–	66.8%	–	81.0%	89.8%	–	–
ACEi/ARB	–	25.2%	–	76.9%	–	51.1%	60.8%	–	–
PPI	–	11%	–	30.6%	–	–	64.2%	–	0.9%

[a]CHANCE—Total study population was 5170. The population included in our analysis is 4696, as per patient-level meta-analysis by Pan *et al*.
[b]GLOBAL LEADERS—Monotherapy with aspirin or ticagrelor during months 13–24 of the study period.
[c]CHANCE—Monotherapy with aspirin from day 1 to 90 and with clopidogrel from day 22 to 90.
ACEi = angiotensin-converting-enzyme inhibitor, ARB = angiotensin receptor blockers, CABG = coronary artery bypass grafting, CKD = chronic kidney disease, MI = myocardial infarction, PAD = peripheral arterial disease, PCI = percutaneous coronary intervention, PPI = proton-pump inhibitors, SD = standard deviation, TIA = transient ischemic attack.

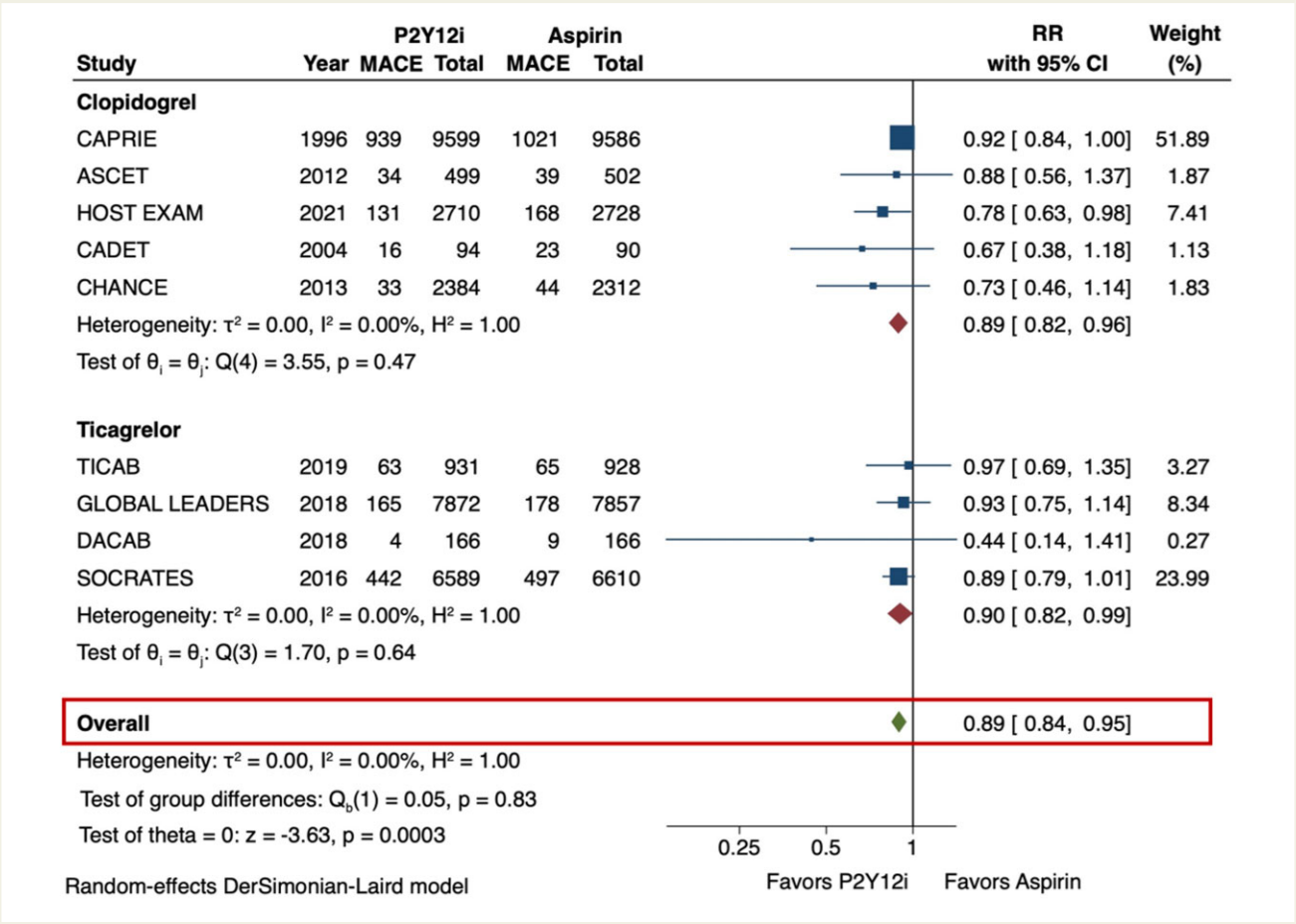


Figure 2 Major adverse cardiovascular events (MACE) in $P2Y_{12}$ inhibitor monotherapy versus aspirin monotherapy. The primary efficacy outcome of interest was MACE, which was defined as a composite of stroke, myocardial infarction (MI), or death in the majority of studies. The DerSimonian and Laird random-effects model was used to examine the risk ratios (RR). All 9 trials were included for this analysis. $P2Y_{12}$ inhibitor monotherapy reduced the risk of MACE by 11% as compared with aspirin monotherapy (RR 0.89 [95% CI 0.84-0.95], $I^2 = 0\%$). This result was consistent irrespective of the $P2Y_{12}$ inhibitor used (p-interaction = 0.83). CI = confidence interval, MACE = major adverse cardiovascular events, P2Y12i = $P2Y_{12}$ inhibitor, RR = risk ratio.

associated with a reduced risk of MI as compared with aspirin (RR 0.81 [95% CI 0.71–0.92], $I^2 = 0\%$, NNT 273) (*Figure 4*). No significant difference was observed in the risk of stroke (RR 0.85 [95% CI 0.73–1.01], $I^2 = 43.3\%$) (*Figure 5*) or all-cause death (RR 1.01 [95% CI 0.92–1.11], $I^2 = 0\%$) (*Figure 6*). The risk of major bleeding (RR 0.94 [95% CI 0.72–1.22), $I^2 = 42.6\%$) (*Figure 3*) and any bleeding (RR 1.07 [95% CI 0.88–1.30], $I^2 = 60.5\%$) were similar between $P2Y_{12}$ inhibitor monotherapy and aspirin monotherapy treatment groups. Bleeding outcomes are expanded in Supplementary material online, *Table S4*.

Subgroup analyses based on the qualifying event (see Supplementary material online, *Figures S1–S3*) revealed that the overall reduction in MACE with $P2Y_{12}$ inhibitors was driven by a reduction in recurrence of the primary event. The risk of recurrent stroke or transient ischemic attack was lower with $P2Y_{12}$ inhibitors as compared with aspirin (RR 0.89 [95% CI 0.81-0.98], $I^2 = 0\%$). Similarly, in patients with coronary artery disease, the risk of MI was lower with $P2Y_{12}$ inhibitors as compared with aspirin (RR 0.83 [95% CI 0.71–0.98], $I^2 = 2.6\%$). As compared with aspirin, $P2Y_{12}$ inhibitors significantly reduced the risk of MI in patients treated with PCI (RR 0.73 [95% CI 0.55–0.96], $I^2 = 0\%$) (see Supplementary material online, *Figure S4*). The risk of major bleeding remained similar across all subgroups (see Supplementary material online, *Figure S5*).

Sensitivity analysis showed that the reductions in MACE (see Supplementary material online, *Figure S6*) and MI (see Supplementary material online, *Figure S7*) were consistent after eliminating the included studies one-by-one. Additionally, meta-regression analyses did not find any significant interaction with the duration of follow-up. The degree of heterogeneity between the studies was low to moderate for all outcomes, except the secondary safety outcome of any bleeding. Funnel plots did not show any significant publication bias (see Supplementary material online, *Figure S8*). The risk of bias assessment of the individual studies was graded between low to some concern (see Supplementary material online, *Table S5*).

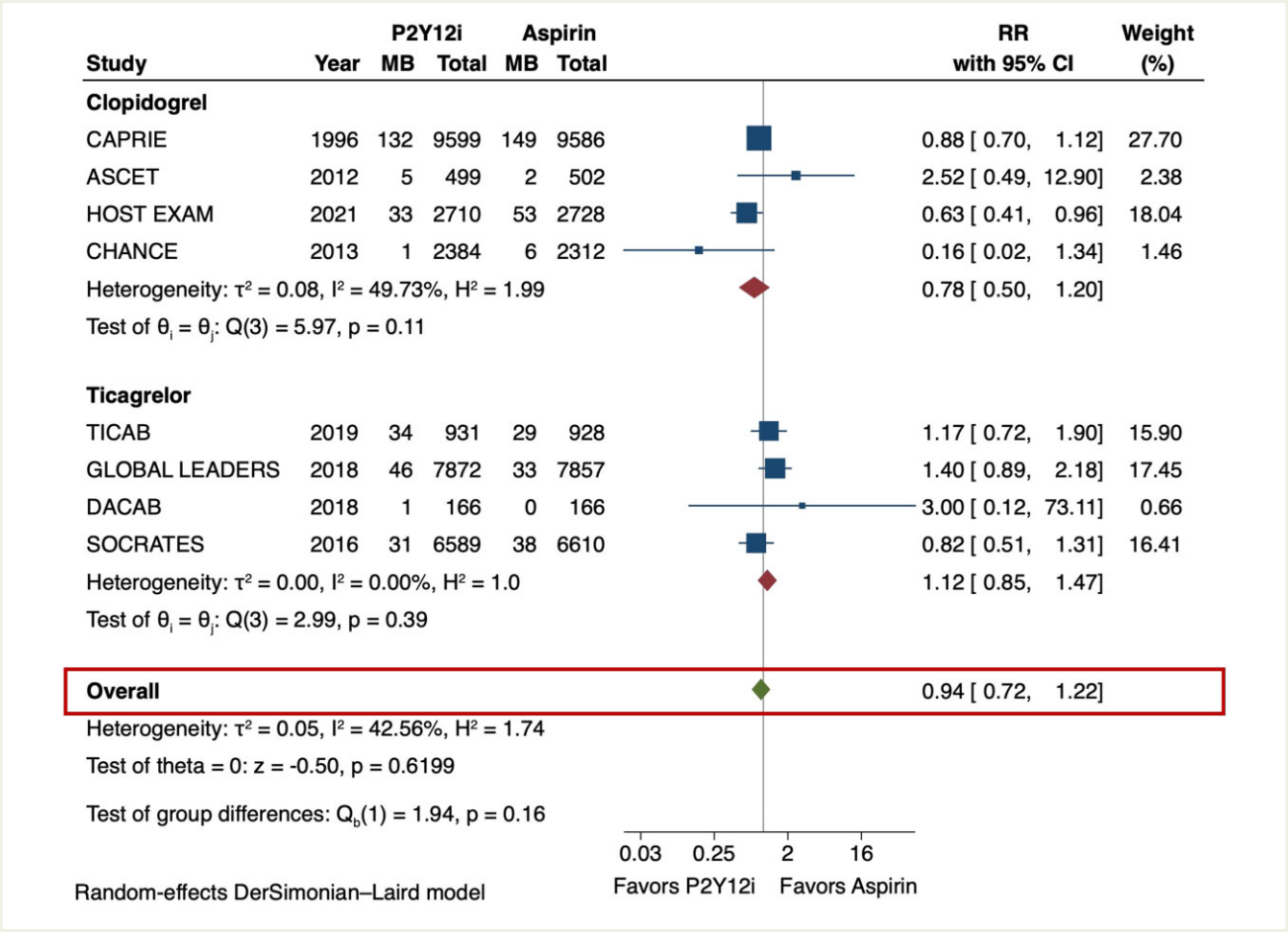


Figure 3 Major bleeding in $P2Y_{12}$ inhibitor monotherapy versus aspirin monotherapy. The primary safety outcome of interest was major bleeding was evaluated using the DerSimonian and Laird random-effects model. There was no significant difference in the risk of major bleeding between $P2Y_{12}$ inhibitor and aspirin monotherapy (RR 0.94 [95% CI 0.72–1.22], $I^2 = 42.6\%$). CI = confidence interval, MB = major bleeding, P2Y12i = $P2Y_{12}$ inhibitor, RR = risk ratio.

Discussion

We conducted an updated meta-analysis of studies comparing $P2Y_{12}$ inhibitor monotherapy with aspirin monotherapy for secondary prevention in patients with established atherosclerotic cardiovascular disease. Our analysis showed that compared with aspirin monotherapy, $P2Y_{12}$ inhibitor monotherapy (with clopidogrel or ticagrelor) significantly reduced the risk of MACE by 11% and MI by 19%. The reduction in MACE was consistent irrespective of the $P2Y_{12}$ inhibitor used and no significant interaction was found between MACE or MI and the qualifying disease/event. We found no significant difference in the risk of major bleeding with $P2Y_{12}$ inhibitor monotherapy compared with aspirin monotherapy. Notably, pre-specified analysis based on the qualifying event showed a greater reduction in the recurrence of the primary event/disease with $P2Y_{12}$ inhibitors. However, the reduction in MACE and recurrent events with $P2Y_{12}$ inhibitor monotherapy did not translate into reduction in all-cause mortality. This may be because of the short duration of follow-up in the majority of trials and may evolve as extended periods of monotherapy with aspirin and $P2Y_{12}$ inhibitors are compared.

Over the past few years, trials demonstrating the feasibility of abbreviated periods of dual antiplatelet therapy after PCI have been under the spotlight.[23–25] However, the evidence regarding the preferred antiplatelet monotherapy to be used following dual antiplatelet therapy has been limited. The CAPRIE trial was the first and largest trial comparing aspirin with a $P2Y_{12}$ inhibitor monotherapy in patients with recent MI, ischemic stroke, or symptomatic peripheral arterial disease.[14] The observed reduction in the occurrence of composite ischemic outcomes with clopidogrel with a lower rate of hospitalization for gastrointestinal bleeding[26] led to its acceptance as an alternative to aspirin. Other small trials that compared aspirin with clopidogrel in patients with chronic ischemic heart disease showed no difference in outcomes.[15,16] Similarly, in patients who underwent CABG, ticagrelor monotherapy was found to be equivalent to aspirin monotherapy in terms of venous graft patency, revascularization, or bleeding.[17,18] Residual risk of recurrent stroke with aspirin monotherapy prompted the SOCRATES trial, a double-blind trial with 13 199 patients that showed similar outcomes with ticagrelor and

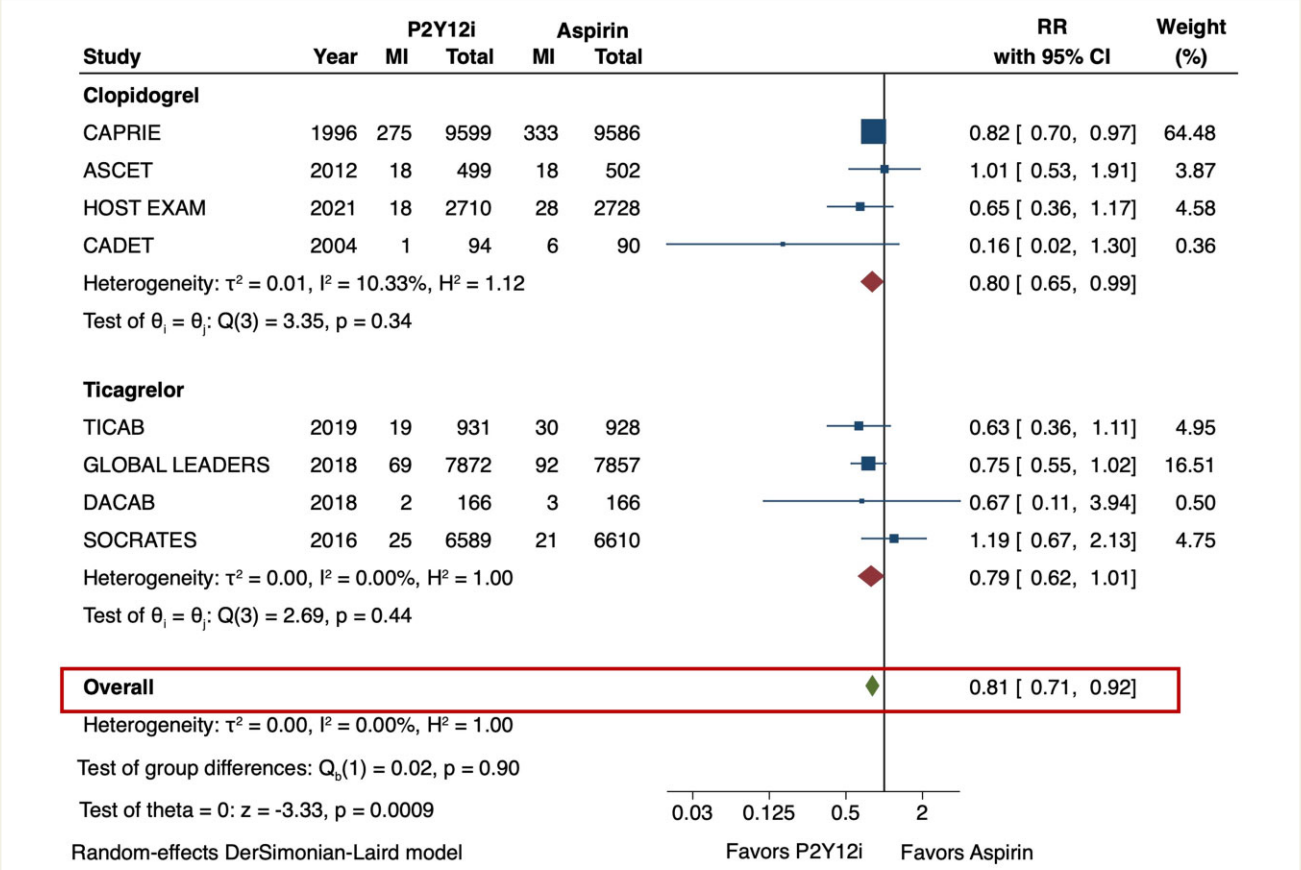


Figure 4 Myocardial infarction (MI) in $P2Y_{12}$ inhibitor monotherapy versus aspirin monotherapy. Pooled risk ratio (RR) of MI was calculated from 8 of the 9 included trials. The use of $P2Y_{12}$ inhibitors was associated with a 19% risk reduction of MI as compared with aspirin (RR 0.81 [95% CI 0.71–0.92], $I^2 = 0\%$). CI = confidence interval, MI = myocardial infarction, P2Y12i = $P2Y_{12}$ inhibitor, RR = risk ratio.

aspirin.[19] Indirect evidence from a network meta-analysis demonstrated no significant difference in ischemic or bleeding outcomes with aspirin versus $P2Y_{12}$ inhibitor monotherapy after a short course of dual antiplatelet therapy in patients post-PCI.[27]

The HOST-Extended Antiplatelet Monotherapy (HOST-EXAM) trial,[22] published in 2021, was the first randomized trial directly comparing aspirin with clopidogrel monotherapy after event-free completion of dual antiplatelet therapy for 6–18 months following PCI with drug-eluting stents. The key finding from this study was lower incidence of the composite outcome of all-cause mortality, MI, stroke, readmission for the acute coronary syndrome, and major bleeding with clopidogrel. However, the short follow-up period (24 months), open-label design, and an exclusively East Asian population limit the generalizability of these results to routine clinical practice. Regardless, this trial has re-energized the debate about the optimal agent for antiplatelet monotherapy for secondary prevention of atherosclerotic cardiovascular events.

A recent meta-analysis by Chiarito *et al* reported a marginal reduction in the risk of MI with $P2Y_{12}$ inhibitor (clopidogrel, ticlopidine, ticagrelor) monotherapy compared with aspirin but found no difference in all-cause mortality, concluding that the available evidence did not support a change in practice away from aspirin.[28] Our study builds on this analysis by (i) including the HOST-EXAM trial, (ii) studying MACE events, and (iii) excluding trials with ticlopidine, hence limiting the analysis to $P2Y_{12}$ inhibitors used in the present day.[29] We chose MACE as the primary outcome since the goal of antiplatelet therapy is the prevention of thrombotic events in all vascular beds and not just coronary, cerebrovascular, or peripheral arterial disease events individually. Moreover, the majority of the included trials were powered for detecting differences in MACE.

Given the observed reduction in the risk of MACE and MI, our analysis may support the preferential use of clopidogrel or ticagrelor over aspirin monotherapy in patients with established atherosclerotic cardiovascular disease. The population to whom our results are most applicable includes patients who have successfully completed 6 to 18 months of dual antiplatelet therapy, patients with chronic coronary syndromes, peripheral arterial disease, and recent ischemic stroke or TIA. Current practice guidelines recommend the use of $P2Y_{12}$ inhibitors as effective alternatives to aspirin monotherapy, but aspirin is still considered the default agent in these scenarios.[30–33] As the evidence demonstrating the equivalency and indeed, the superiority of $P2Y_{12}$ inhibitors is now established, it is reasonable to prefer $P2Y_{12}$ inhibitor monotherapy over aspirin monotherapy. Personalized approach for the choice of $P2Y_{12}$ inhibitor to be used for antiplatelet monotherapy should be considered.

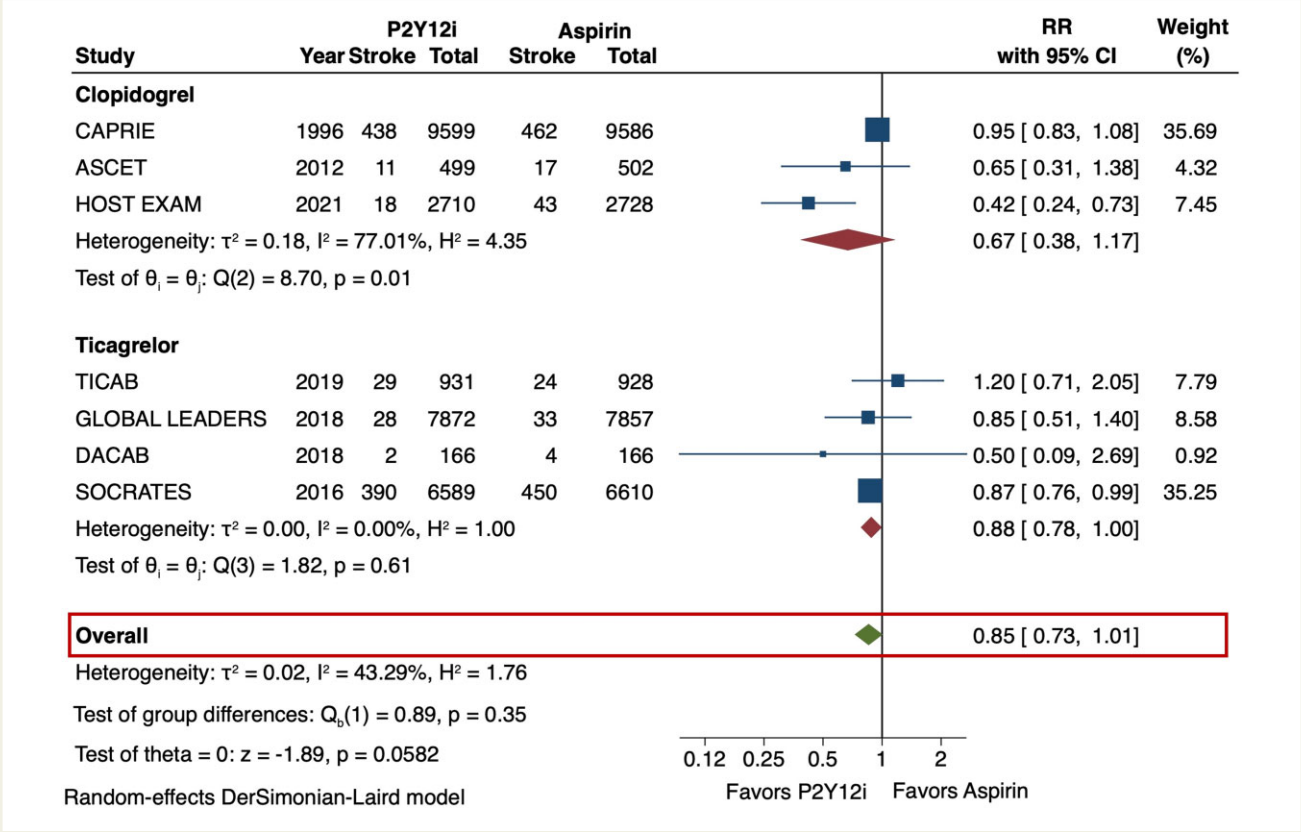


Figure 5 Stroke in P2Y$_{12}$ inhibitor monotherapy versus aspirin monotherapy. The occurrence of stroke (ischemic/hemorrhagic) was reported in 7 trials. No significant difference was observed in the risk of stroke (RR 0.85 [95% CI 0.73–1.01], $I^2 = 43.3\%$). CI = confidence interval, P2Y12i = P2Y$_{12}$ inhibitor, RR = risk ratio.

While routine pharmacogenomic testing for response to clopidogrel is currently not recommended, among patients with established suboptimal response to clopidogrel, other P2Y$_{12}$ inhibitors such as ticagrelor or prasugrel should be favored.[34] Genotype-guided personalized antiplatelet therapy and de-escalation using platelet function testing are options for a more tailored approach, although feasibility and cost-effectiveness are barriers to their widespread use.[35,36] Notably, the cost of ticagrelor may be a barrier to its use in many countries, however, this issue is expected to improve after its patent expires in 2024.

Our study has limitations that should be considered when interpreting the pooled results. The population included in our analysis varied widely and included patients with chronic coronary syndromes, recent MI, cerebrovascular disease, or peripheral arterial disease. To account for this inter-study variability, subgroup analyses were conducted and suggested no significant interaction of qualifying diagnosis with primary or secondary outcomes. However, given the limited number of trials included, the stratified analysis may lack sufficient statistical power to demonstrate possible differences. Similarly, the results from the meta-regression analysis evaluating the role of underlying baseline risk and duration of follow-up might also be limited by the low number of studies included in the pooled analysis. Due to the lack of patient-level data, we were also unable to investigate the effect of background therapies such as statins on the endpoints. The definition of MACE varied marginally between studies but included MI, stroke, and death. While death should ideally be classified as cardiovascular and non-cardiovascular death to capture the potential off-target effects of either drug class, this was not feasible as non-cardiovascular death was reported separately in only 2 studies. Additionally, these findings do not generalize to patients with recent drug-eluting stents requiring dual antiplatelet therapy, patients who had ischemic or bleeding events while on dual antiplatelet therapy, patients with a severe disabling stroke, and patients requiring chronic anticoagulation. The CHANCE trial was designed to compare the outcomes of initial dual antiplatelet therapy for 21 days followed by clopidogrel with aspirin monotherapy after a minor stroke or transient ischemic attack. Although we included outcomes from day 22 onwards, it is possible that the events in the clopidogrel arm were influenced by the lingering effects of dual antiplatelet therapy. We also extracted data selectively from the latter half of the GLOBAL LEADERS trial. We recognize that derivation of data in part may raise doubts about the validity and the decision to include the study. However, the results were consistent upon exclusion of the GLOBAL LEADERS and CHANCE trials (see Supplementary material online, *Table S6*), confirming the robustness of the analyses. Future research directly comparing the outcomes of monotherapy with aspirin versus P2Y$_{12}$ inhibitors for specified indications and head-to-head comparison between different P2Y$_{12}$ inhibitors will help provide definitive evidence.

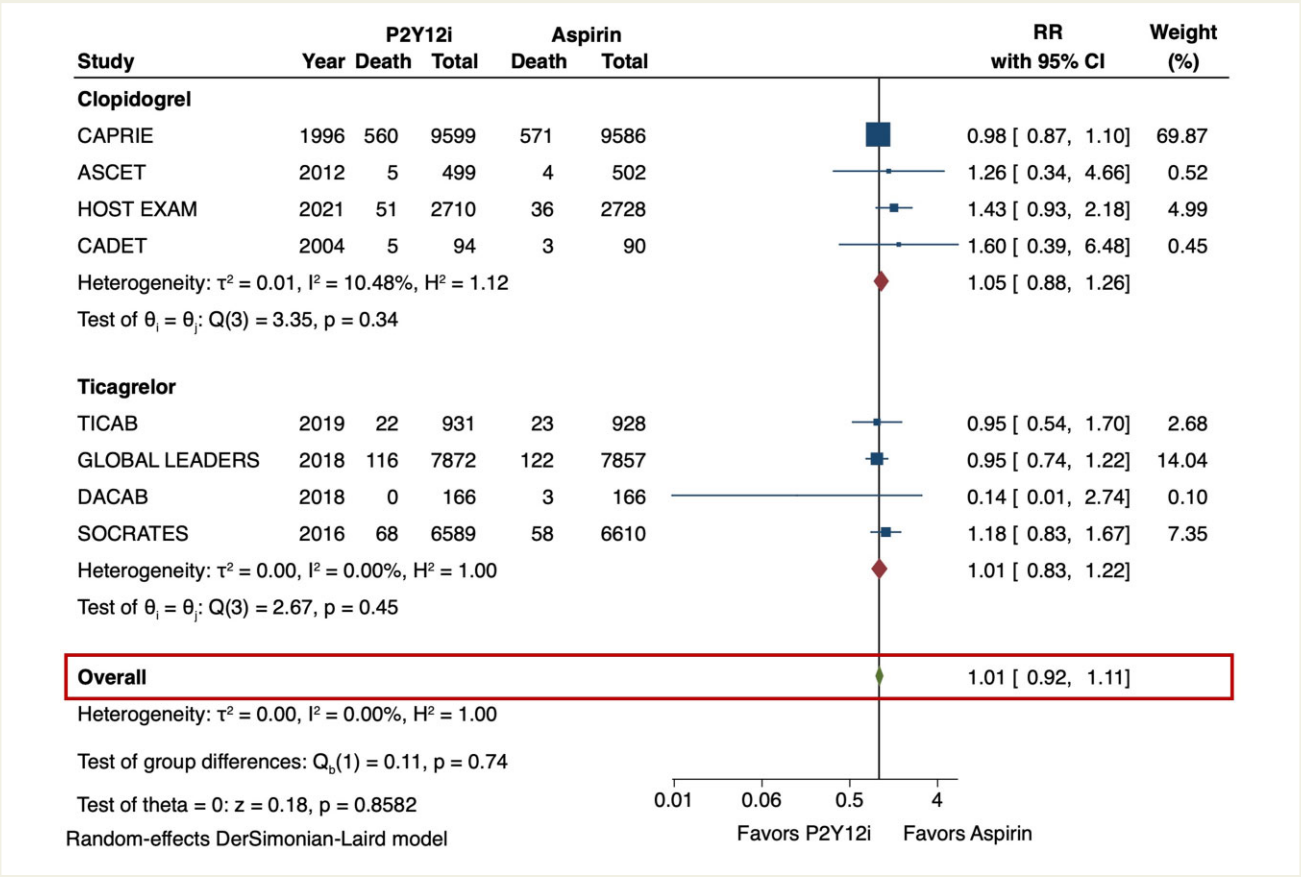


Figure 6 All-cause mortality in $P2Y_{12}$ inhibitor monotherapy versus aspirin monotherapy. All-cause death was analyzed as a secondary outcome from the pooled analysis of 8 studies. Monotherapy with a $P2Y_{12}$ inhibitor or aspirin had similar risks of all-cause death (RR 1.01 [95% CI 0.92–1.11], $I^2 = 0\%$). CI = confidence interval, P2Y12i = $P2Y_{12}$ inhibitor, RR = risk ratio.

In conclusion, in this meta-analysis of randomized trials, $P2Y_{12}$ inhibitor monotherapy for chronic secondary prevention was associated with lower risk of MACE and MI compared with aspirin monotherapy in select patients with established atherosclerotic cardiovascular disease. Dedicated randomized trials comparing the 2 strategies and individual $P2Y_{12}$ agents are needed to further establish the optimal antiplatelet therapy for secondary prevention in patients with atherosclerotic cardiovascular disease.

Lead author biography

Devika Aggarwal completed medical school at Maulana Azad Medical College in New Delhi, India and is currently a resident in Internal Medicine at Beaumont Hospital-Royal Oak in Michigan, USA. She is passionate about pursuing a fellowship in cardiovascular disease followed by a career in academic cardiology. Her current areas of interest include coronary artery disease, antithrombotic therapies, and lipid management.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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Pharma, Regado Biosciences, Stasys; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: Inaugural Chair, American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Boston Scientific (Chair, PEITHO trial), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Novartis, Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol-Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Cowen and Company, Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Piper Sandler, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, CSL Behring, Eisai, Ethicon, Faraday Pharmaceuticals, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Lexicon, Lilly, Medtronic, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Owkin, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi, Stasys, Synaptic, The Medicines Company, 89Bio; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Abbott, Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Philips, Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Takeda. Dr. Qamar reports receiving institutional grant support from Novo Nordisk, NorthShore Auxiliary Research Scholar Fund, NorthShore CardioDiabetes Pilot Grant and fees for educational activities from the American College of Cardiology, Society for Vascular Medicine, Society for Cardiovascular Angiography and Interventions, Janssen and Janssen, Pfizer, Medscape, and Clinical Exercise Physiology Association. All other authors have no disclosures to report.

Data availability

Our data is derived from trials available in the public domain.

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